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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/535,490

05/17/2005

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BU-096XX

3937

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EXAMINER

FORD, VANESSA L

ART UNIT

PAPER NUMBER

1645

MAIL DATE

DELIVERY MODE

12/29/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/535,490	<b>Applicant(s)</b> GENCO ET AL.	
	<b>Examiner</b> VANESSA L. FORD	<b>Art Unit</b> 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 24 September 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 2 and 7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-6 and 8-12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 May 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

**FINAL ACTION**

1. Applicant's amendment and response filed September 24, 2008 are acknowledged. Claim 5 has been amended.

Claims 2 and 7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 21, 2007.

This application contains claim 2 and 7 drawn to an invention nonelected with traverse in the reply filed on December 21, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1, 3-6 and 8-12 are under examination.

***Rejections Withdrawn***

2. In view of Applicant's amendment and response the following rejections have been withdrawn:

a) rejection of claims 1, 3 and 8-9 under 35 U.S.C. 112 second paragraph page 9, paragraph 4.

b) rejection of claims 1, 3 and 8-9 under 35 U.S.C. 112 second paragraph page 9, paragraph 5.

c) rejection of claims 1, 3 and 8-9 under 35 U.S.C. 112 second paragraph, page 10, paragraph 6.

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d) rejection of claim 3 under 35 U.S.C. 112 second paragraph page 10, paragraph 7.

e) rejection of claim 5 under 35 U.S.C. 112 second paragraph page 10, paragraph 8.

### ***Objection/Rejections Maintained***

3. The objection to the specification is maintained for the reasons set forth on pages 2, paragraph 4 of the previous Office Action.

The following objection is maintained and reiterated below:

#### ***Specification Objection***

The specification is objected because of the use of hyperlink on page 9. Hyperlinks can be readily changed and therefore, may not be available to the public. The specification should be reviewed for hyperlinks and the hyperlink must be deleted from the specification.

Applicant has not removed the hyperlink on page 9 of the instant application.

4. The rejection under 35 U.S.C. 112 first paragraph is maintained for claims 3 and 8-9 for the reasons set forth on pages 4-9, paragraph 3 of the previous Office Action.

The following rejection is maintained and reiterated below:

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

#### ***Scope of Enablement***

Claims 3 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for killed whole cell *Porphyromonas gingivalis*, the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the

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amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis* does not reasonably provide enablement for portions or fragments of killed whole cell *Porphyromonas gingivalis*, the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir.1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the relative skill of those in the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In *Wands*, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (*Wands*, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of *Wands* factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The specification teaches that killed whole cell *Porphyromonas gingivalis* or arginine specific proteinases derived from *Porphyromonas gingivalis* (e.g. Arg-gingipain or RGP-1, Lys-gingipain) are the most preferred immunogens used in the claimed

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method (page 9). There is no guidance provided as to which amino acids can be deleted and still have the *Porphyromonas gingivalis* immunogen retain its biological function. Thus, the resulting immunogen could result in a *Porphyromonas gingivalis* immunogen not taught enabled by the specification.

Thomas E. Creighton, in his book, *"Proteins: Structures and Molecular Properties, 1984"*, (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book *"Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in an amino acid's sequence and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide's structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polynucleotide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would not expect any tolerance to multiple

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deletions. There is no guidance provided in the specification with regard to how one would begin to choose “portions or fragments” of the killed whole cell *Porphyromonas gingivalis*, the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis* that would be effective in the claimed method. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which retain the biological activity;
- the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other polypeptides having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptide that are portions or fragments of killed whole cell *Porphyromonas gingivalis*, the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis* that would be effective in the claimed method, in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of deletions or fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the polypeptide's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See *Amgen Inc v Chugai Pharmaceutical Co Ltd.* 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Exparte Forman*, 230 U.S. P.Q. 546(Bd. Pat. & int. 1986).

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In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

#### Applicant Arguments

Applicant refers the Examiner to page 10 of the instant specification. Applicant urges that the teachings of the instant specification was well within the capabilities of those skilled in the art at the time the application was filed.

#### Examiner's Response to Applicant's Comments

Applicant has not defined which amino acids or portions or fragments of the proteins list in the specification on page 10 or otherwise are used in the composition of the claimed method.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in an amino acid's sequence and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide's structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to



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ascertain functional aspects of the polynucleotide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

One of skill in the art would require guidance, in order to make or use polypeptide that are portions or fragments of killed whole cell *Porphyromonas gingivalis*, the capsular polysaccharide of *Porphyromonas gingivalis* or a peptide corresponding to the amino terminus of at least one arginine-specific proteinase derived from *Porphyromonas gingivalis* that would be effective in the claimed method, in a manner reasonable in correlation with the scope of the claims.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

5. The rejection under 35 U.S.C. 102(e) is maintained for claim 1 for the reasons set forth on pages 11-12, paragraph 9 of the previous Office Action.

The following rejection is maintained and reiterated below:

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

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Claim 1 is rejected under 35 U.S.C. 102(e) is anticipated by Barr et al (*U.S. Patent No. 7,204,991 B2 published April 17, 2007*).

Independent claim 1 is directed to a method of therapeutically treating a patient having a symptom of cardiovascular disease comprising the steps of: (a) providing a patient having a symptom of cardiovascular vaccine; and (b) administering to said patient a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *Porphyromonas gingivalis* in a pharmaceutically effective carrier substance.

Barr et al teach methods of administering compositions comprising *Porphyromonas gingivalis* to patients (see the Abstract). Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD). Barr et al teach because of this linkage, compositions comprising *Porphyromonas gingivalis* may also be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3). Barr et al anticipate the claimed invention.

#### Applicant's Arguments

Applicant urges that Barr et al differs from the current patent application in that the endpoint or measure of protection with this protein is different from the endpoint or measure of protection of Applicant's claims. Applicant urges that Barr et al is looking for protection from the formation of abscess on the skin following direct injection of *P. gingivalis* whereas the pending claims are directed at protection from atherosclerosis in response to oral infection with *P. gingivalis*.

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Examiner's Response to Applicant's Arguments

Applicant's arguments filed September 24, 2008 have been fully considered but they are not persuasive. Claim 1 is directed to a method of treating a patient having symptoms of cardiovascular disease comprising administering a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *P. gingivalis*. Barr et al teach because of linkage between periodontal disease and cardiovascular disease (CVD) compositions comprising *Porphyromonas gingivalis* may also be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. Thus, the prior art teaches that comprising *Porphyromonas gingivalis* may be used to treat cardiovascular diseases.

In view of all of the above, this rejection is maintained.

6. The rejection under 35 U.S.C. 102(b) is maintained for claims 8-12 for the reasons set forth on page 12, paragraph 10 of the previous Office Action.

The following rejection is maintained and reiterated below:

Claims 8-12 are rejected under 35 U.S.C. 102(b) is anticipated by Evans et al (*Infection and Immunity*, July 1992, Vol. 60, No.7, p. 2926-2935).

Independent claim 8 is directed to a vaccine against cardiovascular disease comprising a therapeutically effective quantity of an immunogenically effective portion of heat-killed *Porphyromonas gingivalis*.

Evans et al teach a vaccine composition comprising heat-killed whole cells from *Porphyromonas gingivalis* in Freund's incomplete adjuvant (page 2927). Claim limitations such as "said vaccine being effective in preventing or treating atheroma formation" and "said vaccine being effective in preventing or treating atherosclerosis" are being viewed as limitations of intended use. Evans anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's vaccine with the vaccine of the prior art, burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the

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prior art (i.e., that the vaccine of the prior art does not possess the same material structural and functional characteristics of the claimed vaccine). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

#### Applicant's Arguments

Applicant urges that Evans et al describe studies on the use of immunization with an outer membrane protein from *Porphyromonas gingivalis*. Applicant urges that Evans et al uses *Porphyromonas gingivalis* as an antigen. Applicant urges that the differences between Evans et al and the current patent application is that Evans et al looks at the ability of *P. gingivalis* antigens to protect against oral bone loss in a rat model. Applicant urges that the pending claims are directed to protection from atherosclerosis which is a totally different inflammatory process in a different host organ.

#### Examiner's Response to Applicant's Arguments

Applicant's arguments filed September 24, 2008 have been fully considered but they are not persuasive. Independent claim 8 is directed to a vaccine against cardiovascular disease comprising a therapeutically effective quantity of an immunogenically effective portion of heat-killed *Porphyromonas gingivalis*. Evans et al teach a vaccine composition comprising a heat-killed whole cells of *P. gingivalis* in Freund's incomplete adjuvant (page 2977, 1st column). As stated above, claim limitations such as "said vaccine being effective in preventing or treating atheroma formation" and "said vaccine being effective in preventing or treating atherosclerosis" are being viewed as limitations of intended use. A recitation of the intended use of the

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claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

In view of all of the above, the rejection is maintained.

It should be noted that Applicant has address each references individually (Potempa et al, Barr et al and Fletcher et al) and not in combination as presented in the rejections under 35 U.S.C. 103(a).

7. The rejection under 35 U.S.C. 103(a) is maintained for claims 1 and 3 for the reasons set forth on pages 13-15, paragraph 11 of the previous Office Action.

The following rejection is maintained and reiterated below:

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as patentable over Potempa et al (*U.S. Patent No. 6,129,917 published October 2000*) in view of Barr et al (*U.S. Patent No. 7,204,991 B2 published April 17, 2007*).

Independent claim 1 is directed to a method of therapeutically treating a patient having a symptom of cardiovascular disease comprising the steps of: (a) providing a patient having a symptom of cardiovascular vaccine; and (b) administering to said patient a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *Porphyromonas gingivalis* in a pharmaceutically effective carrier substance.

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Potempa et al teach a method of administering to patients immunogenic compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* (see the Abstract). Potempa et al teach that the compositions of the invention may include immunogenic carriers (column 12). Potempa et al teach that compositions of the invention are used to protect animals against *Porphyromonas gingivalis* infections (see the Abstract).

Potempa et al do not teach the claim limitation "treating a patient having a symptom of cardiovascular disease...".

Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD) (column 3).. Barr et al teach because of this linkage, *Porphyromonas gingivalis* may be used to therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* to treat periodontal disease as taught by Potempa et al and cardiovascular disease because Barr et al teach that *Porphyromonas gingivalis* may be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3). It would be expected, absent evidence to the contrary, that compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* or whole cell *Porphyromonas gingivalis* would be effective in treating periodontal disease as well as cardiovascular disease.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease. Thus, it would be obvious to use a known product in a method of treating a cardiovascular symptom to treat a known risk factor or symptom that is ready for improvement to yield predictable results.

Applicant's Arguments

Applicant urges that this patent describes the use of arginine-specific protease of *P. gingivalis* and peptides derived from this protease from protection against *P. gingivalis* infection in a mouse chamber model. Applicant urges the measure of protection with this protein is different from the measure of protection of obtained according to the invention. Applicant urges that Potempa et al is directed to protection from bacterial colonization and from the formation of an abscess on the skin following injection of *P. gingivalis* in a subcutaneous chamber, whereas the pending claims are directed at protection from atherosclerosis in response to oral infection with *P. gingivalis*. Applicant urges that there are differences which the antigen used, the delivery of bacteria and the endpoints of disease.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed September 24, 2008 have been fully considered but they are not persuasive. The claims are directed to a method of therapeutically treating a patient having a symptom of cardiovascular disease comprising the steps of: (a) providing a patient having a symptom of cardiovascular vaccine; and (b) administering to said patient a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *Porphyromonas gingivalis* in a pharmaceutically effective carrier substance.

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In the instant case, Potempa et al teach a method of administering to patients immunogenic compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* (a portion of *Porphyromonas gingivalis*). Potempa et al do not teach the claim limitation the claim limitation "treating a patient having a symptom of cardiovascular disease...".

Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD). Barr et al teach because of this linkage, *Porphyromonas gingivalis* may be used to therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. One of ordinary skill in the art would be motivated to use *Porphyromonas gingivalis* to treat a symptom of cardiovascular disease because Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD) and Barr et al suggest that *Porphyromonas gingivalis* may be of therapeutic benefits in treating cardiovascular disease. To address Applicant's comments regarding atherosclerosis, it should be noted that claims 1 and 3 do not recite that the cardiovascular disease is atherosclerosis.

Applicant is arguing limitations that are not in the claims regarding measures of protection and delivery of bacteria and endpoints of the disease.

In view of the above, there is nothing on the record to suggest that the combination of references do not teach the claimed invention.



8. The rejection under 35 U.S.C. 103(a) is maintained for claims 1 and 3 for the reasons set forth on pages 15-17, paragraph 12 of the previous Office Action.

The following rejection is maintained and reiterated below:

Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as patentable over Potempa et al (*U.S. Patent No. 6,129,917 published October 2000*) in view of Fletcher et al (*U.S. Patent No. 6,585, 977 B1 published July 1, 2003*).

Independent claim 1 is directed to a method of therapeutically treating a patient having a symptom of cardiovascular disease comprising the steps of: (a) providing a patient having a symptom of cardiovascular vaccine; and (b) administering to said patient a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *Porphyromonas gingivalis* in a pharmaceutically effective carrier substance.

Potempa et al teach a method of administering to patients immunogenic compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* (see the Abstract). Potempa et al teach that the compositions of the invention may include immunogenic carriers (column 12). Potempa et al teach that composition of the invention are used to treat periodontal disease (see the Abstract).

Potempa et al do not teach the claim limitation "treating a patient having a symptom of cardiovascular disease...".

Fletcher et al teach that periodontitis (periodontal disease) affects more than 49 million people in the United States and hundreds of millions of people worldwide and has been reported as a risk factor for cardiovascular disease (column 1).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) or the *Porphyromonas gingivalis* mutant to treat periodontal disease as well as cardiovascular disease because Fletcher et al teach periodontitis (periodontal disease) is a risk factor for cardiovascular disease. Thus, one of ordinary skill in the art would reasonably conclude that treating periodontal disease would reduce the risk of cardiovascular disease. It would be expected, absent evidence to the contrary, that a composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or the *Porphyromonas gingivalis* mutant as taught by Fletcher et al would be effective in treating periodontal disease as well as cardiovascular disease.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that

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"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease. Thus, it would be obvious to use a known product in a method of treating a cardiovascular symptom to treat a known risk factor or symptom that is ready for improvement to yield predictable results.

#### Applicant's Arguments

Applicant urges that this patent is directed to a mutant strain of *P. gingivalis* in the recA gene. Applicant urges that the mutant was used as an immunogen and was shown to protect against the same symptoms in a subsequent challenge with another strain of *P. gingivalis*. Applicant urges that the measure of protection described in Evans et al is also different from the measure of protection claimed herein. Applicant urges that Fletcher et al is directed to protection from bacterial colonization and from the formation of an abscess on the skin following injection of *P. gingivalis* in a subcutaneous chamber, whereas the pending claims are directed to protection from atherosclerosis in response to oral infection with *P. gingivalis*.

Applicant urges that immunization to prevent infection-accelerated atherosclerosis is not a logical extension of previous studies performed in the area of infection-atherosclerosis specifically because a consensus has not been established among those skilled in the art at the time the application was filed supporting the contention that any infectious agent or the disease it causes could provide an increased risk for atherosclerosis. Applicant urges that the four references discussed above do not examine any aspect of the immunization to prevent infection-accelerated atherosclerosis.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed September 24, 2008 have been fully considered but they are not persuasive. The claims are directed to a method of therapeutically treating a patient having a symptom of cardiovascular disease comprising the steps of: (a) providing a patient having a symptom of cardiovascular vaccine; and (b) administering to said patient a therapeutic amount of an immunogenic composition comprising an immunogenically effective portion of *Porphyromonas gingivalis* in a pharmaceutically effective carrier substance.

In the instant case, Potempa et al teach a method of administering to patients immunogenic compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* (a portion of *Porphyromonas gingivalis*). Potempa et al do not teach the claim limitation the claim limitation "treating a patient having a symptom of cardiovascular disease...".

Fletcher et al teach that periodontitis (periodontal disease) affects more than 49 million people in the United States and hundreds of millions of people worldwide and has been reported as a risk factor for cardiovascular disease.

One of ordinary skill in the art would be motivated to use *Porphyromonas gingivalis* to treat a symptom of cardiovascular disease Fletcher et al teach that periodontitis (periodontal disease) affects more than 49 million people in the United States and hundreds of millions of people worldwide and has been reported as a risk factor for cardiovascular disease.

To address Applicant's comments regarding atherosclerosis, it should be noted that claims 1 and 3 do not recite that the cardiovascular disease is atherosclerosis.

Applicant is arguing limitations that are not in the claims regarding measures of protection, bacterial colonization, delivery of bacteria and endpoints of the disease.

To address Applicant's urges regarding immunization to prevent infection-accelerated atherosclerosis, it is well known in the art that there is a linkage between periodontal disease and cardiovascular disease. Thus, it would be obvious to use a known product (*Porphyromonas gingivalis*) in a method of treating a cardiovascular symptom to treat a known risk factor or symptom that is ready for improvement to yield predictable results.

The current application was filed on May 17, 2005 and has an effective filing date of November 18, 2002. It was known in the art that there was a correlation between periodontal disease and cardiovascular disease as early as 1988. See Herzberg, MC et al, July 1988. This reference is cited on Applicant's information disclosure statement filed May 17, 2005.

In view of the above, there is nothing on the record to suggest that the combination of references do not teach the claimed invention.

9. The rejection under 35 U.S.C. 103(a) is maintained for claims 4 and 5 for the reasons set forth on pages 17-19, paragraph 14 of the previous Office Action.

The following rejection is maintained and reiterated below:

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as patentable over Potempa et al (*U.S. Patent No. 6,129,917 published October 2000*) in view of Barr et al

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(U.S. Patent No. 7,204,991 B2 published April 17, 2007) as applied to claims 1 and 3 and further in view of Strandberg et al (*Arterioscler Thromb Vasc Biol.*, April 2000, p. 1057-1060).

Claims 4 and 5 are directed to the method of claim 1, wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient.

Potempa et al and Barr et al have been described previously.

Potempa et al and Barr et al do not teach claim limitations the method of claim 1, wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient.

Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals (see the Abstract). Strandberg et al teach that the basic process of most cardiovascular disease, atherosclerosis is now considered to be partly an inflammatory disorder (page 1057). Strandberg et al teach that elevated C-reactive protein have been predicted coronary events in middle-aged women and men (page 1057).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* to periodontal disease and cardiovascular disease (e.g. atherosclerosis) in patients with elevated C-reactive protein levels because Barr et al teach that *Porphyromonas gingivalis* may be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3). Also, Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals.

It would be expected, absent evidence to the contrary, that compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or whole cell *Porphyromonas gingivalis* as taught by Barr et al would be effective in treating periodontal disease as well as atherosclerosis.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease such as atherosclerosis. It is known in the art that elevated C-reactive protein is a predictor of cardiovascular events. Thus, it would be obvious to use a known product in a method to treat known risk factors or symptoms associated with cardiovascular disease that is ready for improvement to yield predictable results.

The combination of Potempa et al and Barr et al have been described above.

In the this rejection Potempa et al and Barr et al are used in combination with Strandberg et al. Applicant did not address this reference in their response.

This reference was used to address the claim limitations " wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient".

Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals. Strandberg et al teach that the basic process of most cardiovascular disease, atherosclerosis is now considered to be partly an inflammatory disorder.

One of ordinary skill in the art would have been motivated to use C-reactive protein in a method of treating symptoms of cardiovascular disease comprising administering to the patient *Porphyromonas gingivalis* because Barr et al teach that *Porphyromonas gingivalis* may be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD and Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals. Strandberg et al teach that the basic process of most cardiovascular disease, atherosclerosis is now considered to be partly an inflammatory disorder.

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10. The rejection under 35 U.S.C. 103(a) is maintained for claims 4 and 5 for the reasons set forth on pages 19-21, paragraph 15 of the previous Office Action.

The following rejection is maintained and reiterated below:

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as patentable over Potempa et al (*U.S. Patent No. 6,129,917 published October 2000*) in view of Fletcher et al (*U.S. Patent No. 6,585, 977 B1 published July 1, 2003*) as applied to claims 1 and 3 and further in view of Strandberg et al (*Arterioscler Thromb Vasc Biol., April 2000, p. 1057-1060*).

Claims 4 and 5 are directed to the method of claim 1, wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient.

Potempa et al and Fletcher et al have been described previously.

Potempa et al and Fletcher et al do not teach claim limitations the method of claim 1, wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient.

Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals (see the Abstract). Strandberg et al teach that the basic process of most cardiovascular disease, atherosclerosis is now considered to be partly an inflammatory disorder (page 1057). Strandberg et al teach that elevated C-reactive protein have been predicted coronary events in middle-aged women and men (page 1057).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* or an immunogenic composition comprising the *Porphyromonas gingivalis* mutant of Fletcher et al to treat periodontal disease and cardiovascular disease (e.g. atherosclerosis) in patients with elevated C-reactive protein levels because Fletcher et al teach periodontitis (periodontal disease) is a risk factor for cardiovascular disease. Thus, one of ordinary skill in the art would reasonably conclude that treating periodontal disease would reduce the risk of cardiovascular disease. It would be expected, absent evidence to the contrary, that a composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or the *Porphyromonas gingivalis* mutant as taught by Fletcher et al would be effective in treating periodontal disease as well as cardiovascular disease. Also, Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals. It would be expected, absent evidence to the contrary, that compositions comprising the *Porphyromonas gingivalis* mutant and the *Porphyromonas gingivalis* compositions would be effective in treating periodontal disease as well as atherosclerosis.

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Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease such as atherosclerosis. It is known in the art that elevated C-reactive protein is a predictor of cardiovascular events. Thus, it would be obvious to use a known product in a method to treat known risk factors or symptoms associated with cardiovascular disease that is ready for improvement to yield predictable results.

The combination of Potempa et al and Fletcher et al have been described above.

In the this rejection Potempa et al and Fletcher et al are used in combination with Strandberg et al. Applicant did not address this reference in their response.

This reference was used to address the claim limitations " wherein said symptom of cardiovascular disease is an elevated level of C-reactive protein and wherein the said symptom of cardiovascular disease is atherosclerosis in said patient".

Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals. Strandberg et al teach that the basic process of most cardiovascular disease, atherosclerosis is now considered to be partly an inflammatory disorder.

One of ordinary skill in the art would have been motivated to use C-reactive protein in a method of treating symptoms of cardiovascular disease comprising administering to the patient *Porphyromonas gingivalis* because Fletcher et al teach periodontitis (periodontal disease) is a risk factor for cardiovascular disease and



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Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals. Strandberg et al teach that the basic process of most cardiovascular disease, atherosclerosis is now considered to be partly an inflammatory disorder.

11. The rejection under 35 U.S.C. 103(a) is maintained for claim 6 for the reasons set forth on pages 21-23, paragraph 16 of the previous Office Action.

The following rejection is maintained and reiterated below:

Claim 6 is rejected under 35 U.S.C. 103(a) as patentable over Potempa et al Barr et al and Strandberg et al as applied to claims 1 and 3-5 above and further in view of P. Amarenco et al (*New England Journal of Medicine*, May 9, 1996).

Claim 6 is directed to the method of claim 1, wherein said patient has atheroma formation in the aortic arch.

Potempa et al Barr et al and Strandberg et al have been described previously.

Potempa et al Barr et al and Strandberg et al do not teach the claim limitation the method of claim 1, wherein said patient has atheroma formation in the aortic arch.

P. Amarenco et al teach that atherosclerotic disease of the aortic arch is a risk factor for recurrent ischemic stroke (cardiovascular disease)(see the Title and the Abstract). P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events (see the Abstract).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* to treat periodontal disease and cardiovascular disease (e.g. atherosclerosis) in patients with elevated C-reactive protein levels and atheroma formation in the aortic arch because Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD) and that *Porphyromonas gingivalis* may be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. (column 3). Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals and P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events. It would be expected, absent evidence to the contrary, that compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or whole cell *Porphyromonas gingivalis* as taught by Barr et al would be effective in treating periodontal disease as well as atherosclerosis in patients that have elevated C-

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reactive proteins and atheroma formation in the aortic arch based on the combination of teachings provided in the prior art.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease such as atherosclerosis. It is also known in the art that elevated C-reactive protein and atheroma formation in the aortic arch are predictors of cardiovascular events. Thus, it would be obvious to use a known product in a method to treat known risk factors or symptoms associated with cardiovascular disease that is ready for improvement to yield predictable results.

The combination of Potempa et al, Barr et al and Strandberg et al have been described above.

In the this rejection Potempa et al, Barr et al and Strandberg et al are used in combination with P. Amarenco et al. Applicant did not address this reference in their response.

This reference was used to address the claim limitations " wherein said patient has atheroma formation in the aortic arch".

P. Amarenco et al teach that atherosclerotic disease of the aortic arch is a risk factor for recurrent ischemic stroke (cardiovascular disease). P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events.

One of ordinary skill in the art would be motivated to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or

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Lys-gingipain) of *Porphyromonas gingivalis* to treat periodontal disease and cardiovascular disease (e.g. atherosclerosis) in patients with elevated C-reactive protein levels and atheroma formation in the aortic arch because Barr et al teach that there is a linkage between periodontal disease and cardiovascular disease (CVD) and that *Porphyromonas gingivalis* may be used in therapy to reduce the incidence or severity of CVD or as an adjunct in treating CVD. Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals and P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events.

There is nothing of record to suggest that the combination of reference do not teach the claimed invention.

12. The rejection under 35 U.S.C. 103(a) is maintained for claim 6 for the reasons set forth on pages 24-26, paragraph 17 of the previous Office Action.

The following rejection is maintained and reiterated below:  
Claim 6 is rejected under 35 U.S.C. 103(a) as patentable over Potempa et al, Fletcher et al and Strandberg et al as applied to claims 1 and 3-5 above and further in view of P. Amarenco et al (*New England Journal of Medicine*, May 9, 1996).

Claim 6 is directed to the method of claim 1, wherein said patient has atheroma formation in the aortic arch.

Potempa et al, Fletcher et al and Strandberg et al have been described previously.

Potempa et al, Fletcher et al and Strandberg et al do not teach the claim limitation the method of claim 1, wherein said patient has atheroma formation in the aortic arch.

P. Amarenco et al teach that atherosclerotic disease of the aortic arch is a risk factor for recurrent ischemic stroke (cardiovascular disease)(see the Title and the Abstract). P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma

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formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events (see the Abstract).

It would have been *prima facie* obvious at the time the invention was made to use an immunogenic composition *Porphyromonas gingivalis* mutant or the *Porphyromonas gingivalis* to treat periodontal disease and cardiovascular disease (e.g. artherosclerosis) in patients with elevated c-reactive protein levels and atheroma formation in the aortic arch because Fletcher et al teach periodontitis (periodontal disease) is a risk factor for cardiovascular disease. Thus, one of ordinary skill in the art would reasonably conclude that treating periodontal disease would reduce the risk of cardiovascular disease. Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals and P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events. It would be expected, absent evidence to the contrary, that compositions comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* as taught by Potempa et al or *Porphyromonas gingivalis* mutant as taught by Fletcher et al would be effective in treating periodontal disease as well as artherosclerosis in patients that have elevated c-reactive proteins and atheroma formation in the aortic arch based on the combination of teachings provided in the prior art.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use *Porphyromonas gingivalis* to treat periodontal disease and/or dental infections caused by *Porphyromonas gingivalis*. It is well known in the art that there is a linkage between periodontal disease and cardiovascular disease such as artherosclerosis. It is also known in the art that elevated C-reactive protein and atheroma formation in the aortic arch are predictors of cardiovascular events. Thus, it would be obvious to use a known product in a method to treat known risk factors or symptoms associated with cardiovascular disease that is ready for improvement to yield predictable results.

The combination of Potempa et al, Fletcher et al and Strandberg et al have been described above.

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In the this rejection Potempa et al, Fletcher et al and Strandberg et al are used in combination with P. Amarenco et al. Applicant did not address this reference in their response.

This reference was used to address the claim limitations " wherein said patient has atheroma formation in the aortic arch".

P. Amarenco et al teach that atherosclerotic disease of the aortic arch is a risk factor for recurrent ischemic stroke (cardiovascular disease). P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events.

One of ordinary skill in the art would be motivated to use an immunogenic composition comprising the arginine-specific proteases (e.g. Arg-gingipain and/or Lys-gingipain) of *Porphyromonas gingivalis* to treat periodontal disease and cardiovascular disease (e.g. atherosclerosis) in patients with elevated C-reactive protein levels and atheroma formation in the aortic arch because Fletcher et al teach periodontitis (periodontal disease) is a risk factor for cardiovascular disease. Thus, one of ordinary skill in the art would reasonably conclude that treating periodontal disease would reduce the risk of cardiovascular disease. Strandberg et al teach that C-reactive protein (CRP) reflects inflammation and predicts cardiovascular disease in middle aged individuals and P. Amarenco et al teach that atherosclerotic plaque (e.g. atheroma formation) in the aortic arch are predictors of recurrent brain infarction and other vascular events.

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There is nothing of record to suggest that the combination of reference do not teach the claimed invention.

***Status of Claims***

13. No claims allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Conclusion***

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/  
Examiner, Art Unit 1645  
December 16, 2008

/Robert B Mondesi/  
Supervisory Patent Examiner, Art Unit 1645